CLAIMS

1. The combination of a growth hormone secretagogue and a p38 kinase inhibitor for use in treatment or prevention of a disease associated with deposition of Aβ in the brain.

2. The use, for the manufacture of a medicament for treatment or prevention of a disease associated with deposition of Aβ in the brain, of a growth hormone secretagogue and a p38 kinase inhibitor.

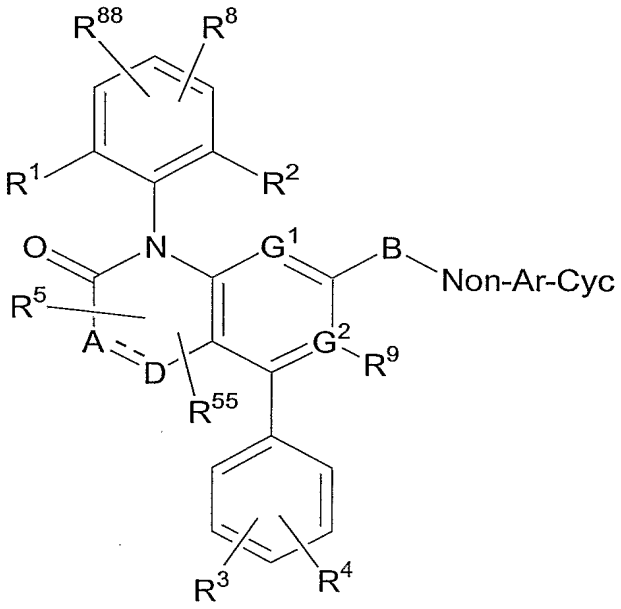
3. Use according to claim 2 wherein the disease is Alzheimer's disease.

4. Use according to claim 3 wherein the medicament is for administration to a patient suffering from MCI.

5. Use according to claim 4 wherein the patient additionally possesses one or more risk factors for developing AD selected from: a family history of the disease; a genetic predisposition to the disease; elevated serum cholesterol; adult-onset diabetes mellitus; elevated baseline hippocampal volume; elevated CSF levels of total tau; elevated CSF levels of phospho-tau; and lowered CSF levels of Aβ(1-42).

6. Use according to any of claims 2-5 wherein the growth hormone secretagogue is N-[1(R)-[(1,2-dihydro-1-methanesulfonylspiro[3H-indole-3,4'–piperidin]-1'-yl)carbonyl]-2-(phenylmethyloxy)ethyl]-2-amino-2-methylpropanamide, or pharmaceutically acceptable salt thereof.

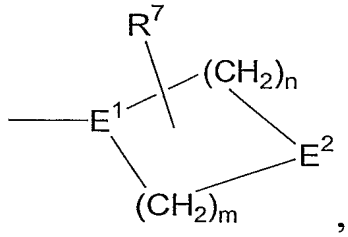
7. Use according to any of claims 2-6 wherein the p38 kinase inhibitor is a compound of formula XI:



(XI)

or pharmaceutically acceptable salts thereof, wherein

Non-Ar-Cyc is



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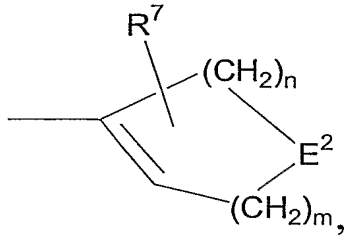

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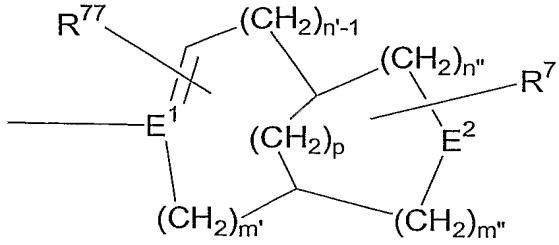

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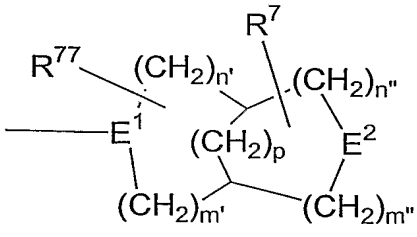

A is N, O, NH, CH_2, or CH;

B is $-C_{1-6}$alkyl–, $-C_{0-3}$alkyl–O–C_{0-3}alkyl–, $-C_{0-3}$alkyl–NH–C_{0-3}alkyl–, $-C_{0-3}$alkyl–NH–C_{3-7}cycloalkyl–, $-C_{0-3}$alkyl–N(C_{0-3}alkyl)–C(O)–C_{0-3}alkyl–, $-C_{0-3}$alkyl–NH–SO_2–C_{0-3}alkyl–, $-C_{0-3}$alkyl–, $-C_{0-3}$alkyl–S–C_{0-3}alkyl–, $-C_{0-3}$alkyl–SO_2–C_{0-3}alkyl–, $-C_{0-3}$alkyl–PH–C_{0-3}alkyl–, $-C_{0-3}$alkyl–C(O)–C_{0-3}alkyl, or a direct bond;

D is CH, CH_2, N, or NH; optionally A and D are bridged by -C_{1-4}alkyl- to form a fused bicyclo ring with A and D at the bicyclo cusps;

E^1 is CH, N, or CR^6; or B and E^1 form –CH=C<;

E^2 is CH_2, CHR, C(OH)R NH, NR, O, S, –S(O)–, or $–S(O)_2–$;

G^1 is N, CH, or C(C_{1-3}alkyl);

G^2 is N, CH, or C(C_{1-3}alkyl);

R, R^7 and R^{77} each independently is hydrogen, C_{1-6}alkyl– group, C_{2-6}alkenyl– group, C_{4-6}cycloalkyl-C_{0-6}alkyl– group, N(C_{0-4}alkyl)(C_{0-4}alkyl)–C_{1-4}alkyl–N(C_{0-4}alkyl)– group, –N(C_{0-4}alkyl)(C_{0-4}alkyl) group, C_{1-3}alkyl–CO–C_{0-4}alkyl– group, C_{0-6}alkyl–O–C(O)–C_{0-4}alkyl– group, C_{0-6}alkyl–C(O)–O–C_{0-4}alkyl– group, N(C_{0-4}alkyl)(C_{0-4}alkyl)–(C_{0-4}alkyl)C(O)(C_{0-4}alkyl)– group, phenyl–C_{0-4}alkyl– group, pyridyl–C_{0-4}alkyl– group, pyrimidinyl–C_{0-4}alkyl– group, pyrazinyl–C_{0-4}alkyl– group, thiophenyl–C_{0-4}alkyl– group, pyrazolyl–C_{0-4}alkyl– group, imidazolyl–C_{0-4}alkyl– group, triazolyl–C_{0-4}alkyl– group, azetidinyl–C_{0-4}alkyl– group, pyrrolidinyl–C_{0-4}alkyl– group, isoquinolinyl–C_{0-4}alkyl– group, indanyl–C_{0-4}alkyl– group, benzothiazolyl–C_{0-4}alkyl– group, any of the groups optionally substituted with 1-6 substituents, each substituent independently being –OH, –N(C_{0-4}alkyl)(C_{0-4}alkyl), C_{1-4}alkyl, C_{1-6}alkoxyl, C_{1-6}alkyl–CO–C_{0-4}alkyl–, pyrrolidinyl–C_{0-4}alkyl–, or halogen;

or R^7 together with a bond from an absent ring hydrogen is =O;

n' + n" = n;

m' + m" = m;

n is 1, 2, 3, or 4;

m is 0, 1, 2, 3, or 4;
n+m is 2, 3, 4, 5, or 6;
p is 0, 1, 2, or 3;
R^1, R^2, R^3, R^4, and R^6 are each independently halogen, C_{0-4}alkyl, –C(O)-O(C_{0-4}alkyl), or –C(O)-N(C_{0-4}alkyl)(C_{0-4}alkyl);
R^5 and R^{55} independently is H, CH_3, CH_2CH_3, or absent;
R^{88} and R^8 each is independently –CN, –C_{0-4}alkyl, –C(O)-N(C_{0-4}alkyl)(C_{0-4}alkyl), –C(O)-O-C_{0-4}alkyl or 1,3-dioxolan-2-yl–C_{0-4}alkyl–;
R^9 is –C_{0-4}alkyl, or absent; and
any alkyl is optionally substituted with 1-6 independent halogen or -OH.

8. A pharmaceutical composition comprising in a pharmaceutically acceptable carrier, a growth hormone secretagogue and a p38 kinase inhibitor.

9. A kit comprising a first medicament comprising a growth hormone secretagogue and a second medicament comprising a p38 kinase inhibitor together with instructions for administering said medicaments sequentially or simultaneously to a patient suffering from AD, age-related cognitive decline, MCI, cerebral amyloid angiopathy, multi-infarct dementia, dementia pugilistica or Down syndrome.

10. A method of treatment or prevention of a disease associated with deposition of Aβ in the brain comprising administering to a subject in need thereof a therapeutically effective amount of a growth hormone secretagogue (GHS) in combination with a therapeutically effective amount of a p38 kinase inhibitor.